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Review

Resistance as a Concomitant of Modern Crop Protection*

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Abstract: This paper reviews the impact of resistance to fungicides and insecticides/acaricides on the way crop protection is practised. It is now clear that resistance can develop to virtually any crop-protection product, in any pest, fungal pathogen or even weed. As a limiting factor in crop protection, it is a fact of life. A positive side-effect is the precision with which products are used today, with increasing implementation of Integrated Pest Management (IPM) programmes. This is a vital step towards sustainability. This paper describes: past experiences; current status of resistance; how resistance management influences current crop protection practices; regulatory aspects; and the outlook for the future. It concludes that EU regulations on resistance management must be simple and workable. Chemicals will continue to have a central role in optimising yields from the world's crops, as new tools, including biotechnology, become available for crop protection and resistance management. The crop-protection industry's innovations and product stewardship programmes will contribute to sustainable agriculture. This will provide continued benefits to users, the environment and society.

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1 INTRODUCTION

The issue of resistance is little understood in many circles. For example, the following quotation is from US Vice-President Al Gore:[1]

> '*Pesticides often leave the most resistant pests behind . . . Then . . . the resistant pests multiply . . . soon, enormous quantities of pesticides are sprayed on the crops to kill just as many pests as were there when the process began. Only now the pests are stronger. And all the while, the quantity of pesticides to which we ourselves are exposed continues to increase*'

Is Vice-President Gore correct? Is resistance out of control? Are crops full of monster pests? No, and with the responsible management of resistance it will be possible to ensure that crop protection remains as part of

* Based on a presentation at the Conference 'Resistance '97—Integrated Approach to Combating Resistance' organised by the Institute of Arable Crops Research in collaboration with the SCI Pesticides Group and the British Crop Protection Council and held at Harpenden, Herts, UK on 14–16 April 1997.
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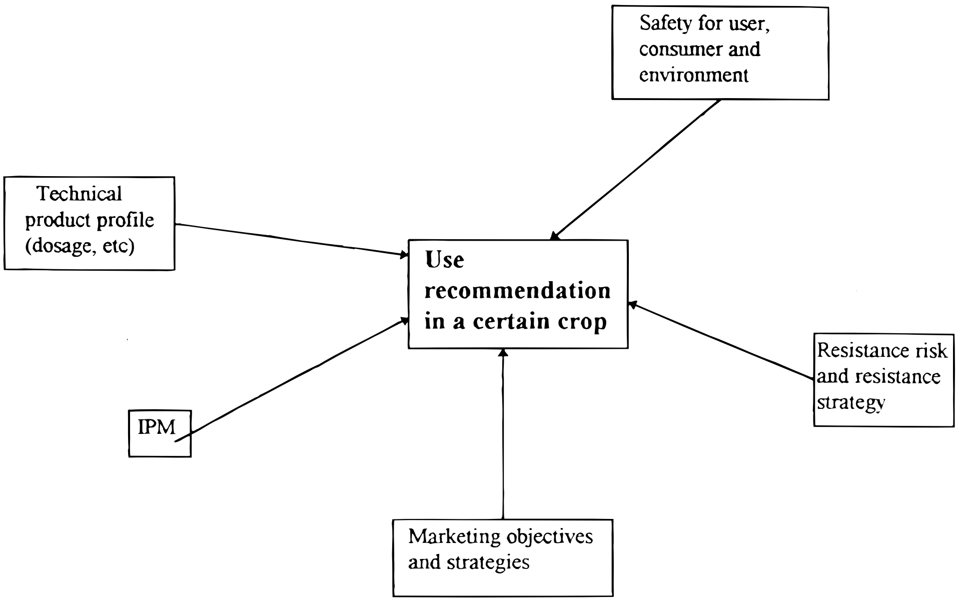

Fig. 1. Design elements of a fungicide use recommendation (from Reference 2).

sustainable agriculture.

Members of the European Crop Protection Association (ECPA) account for more than 90% of Western European sales of crop-protection products. As the pan-European voice of the crop-protection industry, the association currently has 18 full and associate member National Associations and 16 full and associate member companies.

ECPA's major goals are to:

- contribute to the political process leading to new legislation and regulation;
- support sustainable agriculture, in which crop-protection products remain important elements; and
- support Integrated Pest Management (IPM) as part of our efforts to protect the environment.

2 PAST EXPERIENCES

Resistance to crop-protection products springs from nature's reaction to strong and specific selection pressure. For fungicides, it first became a practical problem in the early 1970s with new-generation systemic fungicides. For insecticides and acaricides, resistance was encountered even earlier—examples are DDT and the pyrethroids. In each case, widespread use led to build-up of resistance in target diseases and pests, and to rapid loss of efficacy. More recently, it has become clear that resistance can develop to virtually any crop-protection product, in any pest, fungal pathogen or even weed.

During the 1970s and 1980s, major advances were made in our understanding of how to detect and manage resistance. Key contributors were Charlie Delp, Johann Dekker, Keith Brent and Franz-Josef Schwinn.

This pioneering work set up clearly-defined procedures and approaches to resistance management[2] which are illustrated in Table 1 and Fig. 1. After a, sometimes painful, learning phase, the threat of resistance has been turned into a challenge. As a result, resistance is now largely manageable, and a positive side-effect is the care and precision with which crop protection is practised today. This is a crucial step towards sustainability. Resistance has become part of IPM.

The scientific and technical aspects of resistance were the main focus of the Resistance '97 conference. However, these are not the only perspectives from which to view resistance. There are also practical, economic and social implications to be taken into account. This paper concentrates primarily on these aspects.

TABLE 1
The Concept of Fungicide Resistance Management[a]

1. Definition of objectives
2. Design of procedures and approaches resistance risk assessment design and test of resistance strategies determination of monitoring methods
3. Co-ordination between manufacturers of products with cross-resistance
4. Implementation of use strategies and monitoring methods in practice
5. Ongoing over product lifetime: field monitoring

[a] From Reference 2.

3 STATUS OF FUNGICIDE RESISTANCE

The current status of fungicide resistance is summarised in Table 2. Three interesting points are worth highlighting:

TABLE 2
Current Status of Resistance to Fungicides

Products/ resistance groups	*Resistance risk*[a] + → + + +	*Single/ multiple steps*	*Occurrence of field resistance Practical impact*	*Resistance management strategy*	*Effectiveness of resistance management strategy*[a] + → + + +	
Benzimidazoles	+ + +	Single	Use stopped in many cases (very stable)	Stop use where resistance has occurred Mixtures and alternations	+	Difficult once resistance occurs
Phenylamides	+ + +	Single	Rapid loss with sole use Pre-pack mixtures ± stable	Pre-pack mixtures and limited treatments per season	+ + +	Where strictly followed
DMIs (SBI)	+ +	Multiple	Safety margin eroding	Mixtures (cereals) and spray windows (bananas, apples)	+ +	Problems with reduced and split rates
Morpholines	+ +	Multiple	Safety margin eroding	Mixtures (cereals)	+ +	Problems with reduced and split rates
Dicarboximides	+ +	Single	Loss of control after several years	Limited treatments per season	+	Few alternatives available
Melanin inhibitors	—	?	So far none	None	—	
Anilinopyrimidines	(+ + +)?	Single	So far none	Mixtures and alternations	?	Little experience
Pyrroles	(+ +)?	?	So far none	Mixtures and alternations	?	Little experience
Strobilurins	?	?	So far none	Not yet designed	?	No experience

[a] + + + = high; + = low.

TABLE 3
Current Status of Resistance to Insecticides/Acaricides

Products	*Key pests*	*Risk*[a]	*Region*	*Resistance management activities*
Carbamates	Rice hoppers	++	S E Asia	New products (buprofezine, imidacloprid)
Organophosphates	Rice stem borers	+	S E Asia	Use of fipronil, creation of transgenic *Bt* rice?
	Leptinotarsa decemlineata	++	Poland	IRAC monitoring since 1994
	Bemisia tabaci	+++	Cotton areas	Substitution by buprofezine, imidacloprid, pyriproxifen, diafenthiuron, pymetrozine
Pyrethroids	*Heliothis virescens*, *Heliothis zea*	+++	USA	Rotations with OPs, carbamates, *Bt*, introduction of transgenic *Bt* cotton
	Helicoverpa armigera	+++	Australia	One application window per season, *Bt* cotton
	Leptinotarsa decemlineata	++	Poland	IRAC monitoring since 1994
	Bemisia tabaci	+++	Cotton areas	Same as OPs
Benzoylureas	*Plutella xylostella*	++	Asia-Pacific	IRAC 1995: Product alternation including *Bt*
Chloronicotinyls	Various sucking pests	?[b]		IRAC working group envisaged
Benzoylhydrazides	Various Lepidoptera	?[b]		None yet, deserves close attention
Bacillus thuringiensis(*Bt*)	*Plutella xylostella*	+++[c]	S E Asia, Australia	Use of parasitoids in maintaining *Bt* efficacy?
	Helicoverpa armigera	?[b]	Australia	Under investigation by CSIRO
	Heliothis virescens	?[b]	USA	Under investigation by IRAC-US
Clofentezine, hexythiazox	*Panonychus ulmi*	++	EU	Successful mixtures with diafenthiuron
Mitochondrial electron transport inhibitors[d]	*Tetranychus urticae*	?[b]	USA, EU, Japan	Proposal of Rothamsted-IRAC cross-resistance study needs to be tested in practice
	Panonychus ulmi	?[b]		

[a] +++ = high; + = low.
[b] Risks are expected to increase with more AIs of same type and mode of action entering the market;
[c] Cross-resistance to various *cry*-types in the field appears to be possible;
[d] Fenazaquin, tebufenpyrad, fenpyroximate, pyridaben.

First, the only categories of fungicide which have so far lost substantial market share due to resistance are the benzimidazoles and dicarboximides. The phenylamides, which have a high inherent risk of resistance, have maintained a major market share. This was achieved by using mixtures of phenylamides and conventional protective fungicides, resulting in intervention at different stages of the life cycle of pathogens, with action on both haustoria and spores and activity at two different biochemical sites within the pathogen. The outcome of this strategy was a very stable system. It effectively prevented this product category from being lost, and may well be a useful case study for planning future strategies.

Second, the majority of recent discoveries in the fungicide sector appear to have some risk of resistance. It is industry's experience that only a pro-active and timely approach to resistance management ensures continuing efficacy. Appropriate strategies must therefore be designed and implemented before market launch, and monitoring must follow. It is to be hoped that all companies—including their marketing departments—will co-operate.

Third, the issue of cross-resistance has become less clear-cut. Initially, it was thought that compounds with the same biochemical mode of action would induce resistance in the same way. Now, it appears that cross-resistance is not usually represented in every strain of fungal pathogen. Non-resistant strains can always be found, even for cross-resistance between benomyl and thiabendazole. The exceptions result from different resistance mechanisms which can be specific for individual fungicides within a group.

4 STATUS OF INSECTICIDE/ACARICIDE RESISTANCE

The current status of resistance to insecticides and acaricides is summarised in Table 3. In the 1980s, there were few new product introductions in these two categories, but, during the present decade, promising new chemistry has been developed along with some new niche products. These are very welcome as additional tools to help to manage development of insecticide/acaricide resistance. However, the new chemistry also has inherent resistance risks. In practice, the latter could become a major threat if many products with a similar mode of action were launched, giving greater market penetration.

It is important to note that resistance is not confined only to chemicals. It has also been reported with biologicals such as *Bacillus thuringiensis* Berliner. This is a worrying trend, given the increasingly widespread use of *Bt* endotoxin genes in bioinsecticides and transgenic crops.

It can be concluded that management strategies have today generally brought fungicide resistance under control. Insecticide resistance is more complicated, and the scope for action is more limited. For the future, the Insecticide and Fungicide Resistance Action Committees (IRAC and FRAC) will continue to have a vital role in monitoring the situation and reacting as necessary.

Today, there is a good empirical knowledge of fungicide, insecticide and acaricide resistance. There is also some scientific understanding of its basis. As a result, there has been considerable success in the practical management of resistance. However, it must be accepted that in-depth scientific knowledge is still lacking.

5 RESISTANCE AND ITS INFLUENCE ON CROP-PROTECTION PRACTICES

The key threat related to resistance is that of partial or total loss of efficacy. This has triggered action in the areas of industry, crop-protection practices, regulation and among stakeholders (Table 4). Resistance is far from being a straightforward phenomenon. It does not depend only on a single factor, but, on the contrary, is a complex issue which needs a holistic approach. Solutions can only be found through integrated thinking and action, which must take into account the following:

- scientific and technical aspects, which are themselves highly complex;
- social factors, with communication and co-operation needed between all parties, including companies, academia, extension services and farmers;
- regulatory requirements; and
- liability aspects.

Resistance is also a limiting factor in crop protection. Due to the need for management strategies, it directly influences tactics and choices in the field and has a significant influence at the commercial level. On the technical side, in the field, resistance management strategies often prevent full exploitation of the useful properties of promising new products. It may not be possible to use a systemic or curative product in a technically optimal way—for example by soil application, or with long intervals between sprays—in order to avoid resistance. These limitations also have a major impact on the commercial attractiveness of new products. Approaches such as the use of product mixtures reduce turnover, profitability and return on investment.

On the other hand, thinking in terms of resistance management has positive side-effects. It adds an extra dimension to product stewardship and Responsible Care activities in crop protection. There is increasingly

TABLE 4
Impact and Significance of Resistance in Crop-Protection Practices

Threat of lost efficacy due to resistance			
Industry	*Crop-protection practices*	*Regulations*	*Stakeholders*
Product stewardship and responsible care also for resistance matters R&D investments need payback Liabilities: no damage Commercial limitations due to resistance management accepted Togetherness needed	Limitations to full exploitation of biological properties Need for diversity in control measures	Need for *workable* resistance risk assessment scheme for product registration	Collaboration ⇒ Industry ⇒ Farmers ⇒ Public services ⇒ Academia ⇒ Consultants Basic research Resistance monitoring Support of strategy implementation
↓	↓	↓	↓
Defined approaches and procedures *Voluntary* action and agreements Establishment of RACs and subgroups	More sustainable crop-protection systems Resistance as an example of practical IPM	Industry to make proposal	Resistance as holistic issue Collective action needed Resistance—an integral part of crop protection

careful use of novel molecules, along with more innovative approaches to crop protection, involving mixtures and alternating applications of various products. These approaches form part of IPM programmes; they have a positive impact on the environment, and provide further impetus for optimal product use. They also support the trends in EU agricultural policy towards socially acceptable, environmentally friendly and economic agriculture.

By accepting a leadership role in this issue and by taking rapid voluntary action, industry—along with other institutions and academia—has significantly shaped resistance management. The need to take resistance seriously has been accepted. This is an essential step towards a sustainable future for crop protection technology.

The effort put into developing and implementing resistance management strategies has another useful benefit in that it proves to critics of industry, such as certain non-Governmental Organisations that industry can keep its own house in order. Overall, resistance has been, and continues to be, a major challenge to industry. It is a high priority for companies, and a major influence on how crop protection is practised. As a central aspect of modern crop protection, it remains extremely important.

6 REGULATORY ASPECTS

A concern of our industry is the tendency for over-regulation at EU level. Compared with the situation in the USA we are already heavily regulated, and this is having a negative impact on new product registration. Forty new compounds were registered in the USA in 1995, and 58 were approved in Japan between 1992 and June 1996. In contrast, in the EU, none have been registered since July 1993.

The EU is also lagging behind in terms of time taken to register new active ingredients. In the USA, the minimum time to register a new active ingredient is 24 months, and in Japan, 18 months. Since Directive 91/414 came into force more than three years ago, not a single new active ingredient has been registered at EU level.

Additional burdensome and costly EU regulations for crop-protection products must therefore be avoided. We would like to see a harmonised approach across all OECD countries; this is also our objective for resistance aspects.

The EU Registration Directive (91/414/EEC) says that efficacy data should include 'information on the possible occurrence of the development of resistance.' If resistance is likely, a management strategy must be submitted. The directive sets a framework, but a resistance risk assessment scheme and detailed data requirements have not yet been worked out and agreed. Industry supports the implementation of 91/414, but we have a clear vision of how resistance matters should be dealt with and wish to see a simple, workable system. Experience shows that resistance can be managed using basic studies which industry routinely carries out on new products. Such studies are not excessively complex, costly

or time-consuming, and all the main factors to be taken into account, including inherent product characteristics or management approaches, are well understood.

In terms of regulation for resistance aspects, industry's position is that data requirements should be descriptive, qualitative and straightforward to interpret, which would simplify evaluation by EU member states. They should cover cross-resistance, inherent risks in new products, and resistance management strategies.

Industry will make a proposal based on its extensive experience in resistance management. From this, a resistance risk assessment scheme within 91/414 should be: simple, in order to cope satisfactorily with complex matters; applicable to all types of products; rapid, not delaying market introduction; easy to implement; a help to member states; and based on voluntary action rather than command and control.

The last point is of particular relevance. Current trends in the USA and in certain European markets—such as the UK and Germany—are to move away from command and control and towards voluntary agreements. Excessive regulation always leads to implementation problems in EU Member States, and a lack of efficiency. Environmental legislation and 91/414 are prime examples of this. While voluntary or negotiated agreements might not always go as far as legislation and regulation, they have a higher rate of success because of their relative ease of implementation. This would be the best approach for resistance management.

In the policy arena, proposals will be made this year on reforming the EU Common Agricultural Policy (CAP). Part of the 40 billion ECU which support EU agriculture each year will shift from production-based subsidies to financial support for sustainable, environmentally sound technologies and practices. IPM and resistance management have a good chance of qualifying for such funding.

7 OUTLOOK

Industry is committed to advancing understanding of resistance. A combination of scientific, marketing and communications approaches will be needed. From a scientific viewpoint, there are five areas to improve our scientific base further in the fungicide sector:

Resistance build-up—The contributing factors have been identified, but there is relatively little understanding of how they are interrelated. Information is needed in such areas as: the changes which occur at the molecular level when resistance develops; population dynamics and genetics of resistant or less sensitive strains and epidemiology and fitness of resistant or less sensitive strains.

Cross-resistance aspects—more details are required.

Resistance strategies—these are still largely empirical and not science-based.

Scientific prediction of resistance occurrence—as a consequence of the three above factors, predicting the occurrence of resistance is still in its infancy.

Biotechnology will have a major impact through transgenic crops and improved diagnostic methods to detect and monitor resistance.

From a marketing standpoint, additional tools are now becoming available for crop protection and resistance management. The various options are as follows:

Transgenic disease- and pest-resistant crops—resistance may also be an issue here. For example, plants which produce toxins throughout the season might pose challenges not yet experienced with chemical crop-protection products. Possible tolerance break-down and cross-resistance must be investigated.

Novel chemistry which does not lead to cross-resistance.

Biological products.

Products which activate plants' natural resistance mechanisms—these appear to have a low resistance risk.

Only cautious integration of these approaches will ensure that resistance remains within control. This will also help ensure a sustainable future for crop protection. The best strategy will be to combine biotechnology with chemistry, and not to play one off against the other.

8 COMMUNICATION

This continues to be vital in resistance management. It has two key aspects, in that internal dialogue within companies is needed to ensure that the need for short-term financial gain is balanced against the longer-term future of products. Also necessary is dialogue between all groups involved. Industry needs to share its experiences with academia, extension services and consultants. The resistance action committees have an important role to play in furthering this dialogue and industry continues to seek further collaboration with other parties.

9 CONCLUSIONS

Resistance, as a limiting factor in crop protection, is a fact of life, and industry has voluntarily taken responsibility for its management and wishes to retain this leadership role. EU regulations on this topic must be simple and workable; industry will shortly be making specific proposals on resistance risk assessment and data requirements.

The need for resistance management has a positive influence on the care with which crop protection is practised. It goes hand-in-hand with tools like Good

Agricultural Practice and Integrated Pest Management in ensuring sustainability.

In future, increasing numbers of tools will be available for managing resistance. Chemicals will continue to have a central role in optimising yields from the world's crops for the future. The crop protection industry's innovations and product stewardship programmes will contribute to sustainable agriculture and this will provide continued benefits to users, the environment and society as a whole.

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